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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/822,231	03/26/2004	Gregory Alan Lazar	A-71386-8	1316

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EXAMINER	
CROWDER, CHUN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 04/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/822,231	LAZAR ET AL.	
	Examiner	Art Unit	
	Chun Crowder	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *8-12,14-16,18-20 and 37-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 13, 17 and 21-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

2. Applicant's election without traverse of Group I and species of IgG1, position 332E, and non-engineered glycoforms, filed 12/13/2005, is acknowledged.

The numbering of amended claims is not accordance with 37 C.F.R. 1.126. The original numbering of the claims must be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When claims are added, except when presented in accordance with 37 CFR 1.121(b), they must be renumbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 33 (the second claim 33) to claim 34 have been renumbered 34-35.

Claims 1-36 have been amended.
Claims 38-42 have been added.
Claims 1-42 are pending.

Claims 8-12, 14-16, 18-20, and 37-42 are withdrawn from further consideration by the Examiner, under 37 C.F.R. 1.142(b), as being drawn to nonelected inventions.

Claims 1-7, 13, 17 and 21-36 are currently under consideration to the extend that claims read on elected invention and species.

3. Applicant's claim for domestic priority under 35 U.S.C. 119(e) and 120 is acknowledged. The priority applications 10/672,280, 10/379,392, 60/477,839, 60/467,606, and 60/442,301 upon which benefit is claimed appear to provide adequate support under 35 U.S.C. 112 for subject matter claimed in the instant application.

However, the provisional application 60/414,433 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-7, 13, 17 and 21-36 of the instant application. Specifically, insufficient support was identified for the limitation of "position 332" of the Fc region. Consequently, the claims have been accorded the priority of the USSNs: 10/672,280, 10/379,392, 60/477,839, 60/467,606, and 60/442,301.

4. The application is required to be reviewed and all spelling, TRADEMARK, and like error corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent application, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

5. Claims 1, 17, 22-31 are objected to because of the following informalities. Claim 1 has an additional "an" at the beginning of the claim. Claims 17, 22-31 recite "CDC", and/or "ADCP". It is suggested that applicant amend the claims to recite the full names of the "CDC", and/or "ADCP".

Appropriate correction is required.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 21-23, 28, and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21-23, 28, and 33 are indefinite in its recitation of "modulate" because it is ambiguous as to the direction (positive or negative) or degree of the effect of the said "modulate". The term "modulate" is not defined by the claims, the specification does not provide a standard form ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-7, 13, 17, 21-33, and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A) Claims 1-7, 13, 17, 21-33, and 36 recite "Fc variant" as part of the invention.

The specification discloses on pages 30-31 that a "Fc variant" according to the definition of a variant polypeptide meant an Fc sequence that differs from a parent Fc sequence by at least one amino acid modification, e.g. from about one to about ten amino acid modification, or possess at least 80% homology with a parent polypeptide sequence.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention. The disclosure appears to show only antibodies with certain specified amino acid substitutions. For example, the specification discloses only engineered antibodies such as rituximab, alemtuzumab an anti-CD20 antibody with amino acid substitutions in the Fc region (see Figures 3-38 of the specification as-filed). The instant claims encompass in their breadth *any* variant Fc comprising with at least one amino acid substitution.

However, there does not appear to be sufficient guidance in the specification as field as to how the skilled artisan would make and use the claimed "variant Fc". The state of the art at the time the invention was made recognized that even single amino acid differences can result in drastically altered function of antibodies. For example, Lund et al. (The Journal of Immunology 1996, 157:4963-4969) show that even a single amino acid replacement within the CH2 domain of IgG can alter the glycosylation profile of an antibody therefore influence its effector functions of Fc receptor binding and complement activation (see entire document, particularly Discussion on pages 4966-4968). Further, Lazar et al. (WO 03/074679) teach that the determinants of antibody properties, such as stability, solubility and affinity for antigen, important to its functions are overlapping; thus engineering an antibody to be more soluble may cause a loss in affinity for its antigen (see entire document, particularly page 3).

Given the extensive variation permitted by the instant claim language, the skilled artisan would not reasonably predict such "Fc variant" to have the same function as the instant claimed invention.

Reasonable correlation must exist between the scope of the claims and scope to enablement set forth. Applicant does not appear to provide guidance as to other "Fc variant" which meets the claimed limitation of exhibits altered binding to an FcγR.

In addition, it is unpredictable if functional activity will be shared by two polypeptides having 80% identity over the full length of their sequences. The specification does not appear to provide sufficient guidance as to which residues should or should not be changed to preserve any particular function. Although the specification does provide working examples of antibodies such as antibodies with position 332 of the Fc region altered (e.g. see Figures 13a, 22a, 22b), the variation permitted by the instant claim language is extensive.

However, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the claimed "Fc variant". The specification provides no direction or guidance regarding how to produce "Fc variant" as broadly defined by the claims.

In view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Applicant is invited to consider amending the claimed Fc variant/polypeptide to antibody and/or Immunoadhesin as disclosed on pages 28-29 of the instant specification to obviate this rejection.

B) Claim 21 recites "effector function" as part of the invention.

The specification does not provide a sufficient enabling description of the claimed invention. The specification only discloses that the "effector function" as antibody dependent cell-mediated cytotoxicity (ADCC), complement dependent cytotoxicity (CDC) and antibody dependent cell-mediated phagocytosis (ADCP) (see pages 27-28 of the specification as filed). The instant claims encompass in their breadth *any* "effector function(s)" mediated by Fc variant.

However, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the antibody variant recited in the instant claims to modulate the "effector function(s)". There is insufficient guidance to direct a person of skill in the art to select particular FcγRs.

For example, It is well known in the art at the time the invention was made that antibody effector functions are mediated through its Fc binding to Fc receptors. While a common set of IgG1 residues is involved in binding to all FcγRs; FcγRII and FcγRIII also utilize residues outside the common set (Shields et al. The Journal of Biological Chemistry, 2001. 276;(9):6591-6604. See entire document, particularly page 6591). Without detailed direction as to which FcγRs is/are involved in the binding of the antibody variant, a person of skill in the art would not be able to determine without undue experimentation which of the "effector function(s)" encompassed by the instant claims other than ADCC, CDC, and ADCP.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the skilled artisan cold not make and use the scope of the Fc variant for modulating "effector function(s)", since the amino acid positions of the Fc region involved in binding of different FcγRs was unpredictable at the time the invention was made. Thus the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

It is suggested to amend the claims to recite the "effector function" encompassed by the claimed Fc variant. See claim 22 for example.

10. Claims 1-7, 13, 17, 21-33, and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following *written description* rejection is set forth herein.

Claims 1-7, 13, 17, 21-33, and 36 recite "Fc variant" as part of the invention.

There is insufficient written description in the specification as-filed of "Fc variant" as recited in the instant claims.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. (See Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, especially page 1106 3rd column). A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. MPEP 2163 II.A.3a.ii.

The claims recite a genus "Fc variant" as part of the invention without providing a physical structure or testable functional activity for the "Fc variant"

The genus of the "Fc variant(s)" are therefore very large. Applicant has disclosed only antibodies with certain amino acid modifications such as position 332 at the Fc region (e.g. see Figures 13a, 22a, 22b). Thus Applicant has disclosed only a limited species of the "Fc variant", namely antibodies. The claimed "Fc variant" lack a common structure essential for their function and the claims do not require any particular structure basis or testable functions be shared by the instant "Fc variants".

It does not appear based upon the limited disclosure of antibodies alone that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the limited number of species disclosed and the extensive variation permitted within the genus of "Fc variant polypeptide".

"Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d, 1398, (Fed. Cir. 1997).

The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406.

In the absence of disclosure of relevant, identifying characteristics of the "Fc variant", there is insufficient written disclosure under 35 U.S.C. 112, first paragraph.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 1115).

Applicant is invited to consider amending the claimed Fc variant/polypeptide to antibody and/or Immunoadhesin as disclosed on pages 28-29 of the instant specification to obviate this rejection.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1-7, 13, 17 and 21-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Lazar et al. (WO 03/074679) (see entire document).

Lazar et al. teach and claim an antibody variant with modification at Fc region for improved physico-chemical properties (see entire document, particularly 3-5). Specifically, Lazar et al, teach that amino acid modifications such as 332E at the Fc region of an antibody contribute to domain stability (e.g. see pages 8-9, Figure 11b, and claims 31-35 in particular). Further, Lazar et al. teach that strategies of amino acid modification at Fc regions can be applied to antibodies against targets including Her2/neu (e.g. see page 63), MUC1(e.g. see page 71) and VEGF (e.g. see page 61), as well as Fc fusion proteins (e.g. see pages 43-44). Furthermore, Lazar et al. teach that the said variants of antibodies can be used in a composition for injections intravenously (e.g. see pages 21-22).

Given the referenced antibody variants have the same amino acid substitution at the same position as the claimed Fc variant, the claimed functional limitations of altered antibody binding affinity to FcγRs and effector functions such as ADCC, CDC and ADCP would be inherent properties of the referenced antibody variants.

Given the teachings of the widespread use as therapeutics, diagnostics, and research reagents (e.g. see page 1) as well as the known therapeutic antibodies such as rhumAb VEGF and Herceptin (e.g. see Figures 14-28), the ordinary artisan would have immediately envisaged that Lazar et al. taught pharmaceutical compositions comprising referenced antibodies with pharmaceutically acceptable carriers.

Therefore, the reference teachings anticipate the claimed invention.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lazar et al. (WO 03/074679) in view of Lam et al. (US Patent 6,171,586).

The teachings of Lazar et al. have been discussed, supra.

Lazar et al. does not teach a pharmaceutical composition with acceptable carrier.

However, it was well know in the art at the time the invention was made that in vivo applications of antibodies requires antibodies to be in solution with pharmaceutically acceptable carriers. The teachings of Lam et al. have been discussed, supra.

It would have been obvious to the ordinary artisan at the time the invention was made to formulate therapeutic antibodies with pharmaceutically acceptable carriers for treating diseases. The ordinary artisan would have been motivated to do so because antibodies for pharmaceutical applications are formulated in preparations including pharmaceutically acceptable carriers.

Given the teachings of Lazar et al. regarding the variants of antibodies with amino acid modification for enhanced stability and their therapeutic usages, and the teachings of Lam et al. formulating therapeutic antibodies with pharmaceutically acceptable carriers for in vivo application, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success in formulating the Fc variant in a pharmaceutically acceptable carrier.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was mad, as evidenced by the references, especially in the absence of evidence to the contrary.

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 1-7, 13, 17 and 21-36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 7, 8, 10-28, 30-41, 43-53, 59, and 61 of copending USSN 10/672,280.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant and the copending application claims are drawn to same or nearly the same polypeptide variants with the same modifications to the Fc regions for altered affinity for FcγRs and effector functions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 1-7, 13, 17 and 21-36 are directed to an invention not patentably distinct from claims 1-5, 7, 8, 10-28, 30-41, 43-53, 59, and 61 of commonly assigned 10/672,280 for the reasons stated above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned 10/672,280, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Crowder whose telephone number is (571) 272-8142. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chun Crowder, Ph.D.
Patent Examiner
February 10, 2006

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TC 1600
2/2/06